REMARKS

The applicant acknowledges finality of the restriction requirement despite its traversal. The applicant has amended the claims accordingly by requiring Z in formula (1) of claim 1 to be CR^4.

The applicant appreciates the initialed copy of the Information Disclosure Sheet that was provided by the Examiner indicating that the disclosed references have been considered.

Claims 1-21 were presented for examination and were variously rejected in a very thorough Office Action. Careful consideration has been given to the grounds for rejection, and the following amendment and discussion are offered in response. Reconsideration, in light of the above amendments and the following comments, is respectfully requested.

The Claims have been amended to remove certain embodiments of Ar from the scope of the claims. The amended description of Ar in claim 1 is based on paragraph [0025] of the specification, and omits phenyl from a list of preferred groups for Ar. Claims depending from claim 1 and further limiting Ar have also been amended to be consistent with this amendment.

Claim 1 was also amended to remove the term 'noninterfering substituent' from the descriptions of certain variables. The groups R^2, R^3 and R^4 are now defined by structural descriptions. The amended descriptions of R^2, R^3 and R^4 are taken from original dependent claims 2 and 3 and thus add no new matter. Claim 1 was also amended to remove the term 'prodrugs,' and to refer to the compounds and their salts in the alternative as suggested by the Examiner. The amendment of claim 1 also deletes O from the groups that X in formula (1) can represent.

Claims 2 and 3 have been canceled in light of the amendments incorporating their content into claim 1. Claim 5 was amended to further limit Ar in a manner consistent with amended claim 1. Claims 8, 11, 16, 18 and 19 were amended to depend from claim 1 in light of the foregoing amendments. Claims 14 and 15 were amended to refer to 'said aromatic moiety of Ar' to obviate any possible confusion over the term 'said aryl' and to ensure that those claims find clear antecedent basis in claim 13.

Claim 17 was amended to require X in the compounds of formula (1) to be NH. Since the original limitation required R^1 to be H, and R^1 would only be present when X represented NR^1, that amendment adds no new matter and is supported by the original claim and by the examples in Table 1. Claim 19 was also amended to indicate that the 4-pyridyl group represented by Ar can be 'optionally substituted'; that is consistent with and supported by claim 1, which allows each embodiment of Ar to be optionally substituted. Claims 22 and 23 were added. Claim 22 is supported by the specification and particularly by the examples in Table 1, most of which include one or two substituents on the phenyl at position 2 of the pyrimidine ring. Claim 23 recites specific conditions that can be treated with the methods and compounds of the invention, and is supported by paragraphs [0004] and [0005] of the application as filed.

No new matter has been added, and entry of the amendment is respectfully requested.

The Rejection Under 35 U.S.C. § 112, Second Paragraph

1.-2. Claims 1-21 were rejected as indefinite for reciting 'salts and prodrugs'. The claims have been amended to delete the term 'prodrugs', and to include salts in the alternative rather than in the conjunctive, to enhance clarity. This amendment is believed to address any alleged indefinitiness issues with respect to those terms, and to clearly indicate that the claims include the neutral compounds and their pharmaceutically acceptable salts.

3. The term 'noninterfering substituent' has been replaced in the claims with structural description taken from the dependent claims, as explained above.

In light of these amendments, the applicant requests that these rejections be withdrawn.

The Rejection Under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 1-21 were rejected because "the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making prodrugs of the claimed compounds." This rejection is believed to be fully addressed by the

amendment of the claims, which removes the term 'prodrug' from the claims. Withdrawal of this rejection is therefore requested.

Claim 20

Claim 20 was specifically rejected under 35 U.S.C. § 112, First Paragraph because "the specification, while being enabling for treating fibrosis of the liver, does not reasonably provide enablement for treating any or all diseases or conditions mediated by TGF-β generically embraced in the claim language." The Office recites a list of conditions that the specification indicates are associated with excessive activity of TGF-β, and then says, "the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host." The applicant traverses this rejection.

First, "highly predictive" is not part of the enablement standard, nor does that standard require the applicant to provide "competent evidence" related to "all the uses disclosed". Enablement requires that one of ordinary skill could practice the invention as claimed without undue experimentation. According to the MPEP, "the scope of enablement must only bear a 'reasonable correlation' to the scope of the claims." MPEP 2164.08, citing *In re Fisher*. Nor does the presence of inoperative embodiments render a claim nonenabled. MPEP 2164.08(b).

In support of this rejection, using cancer as an example, the Office asserts, "Tumors vary from those so benign that they are never treated to those so virulent that all present therapy is useless." Assuming it is true, that statement indicates that those skilled in the medical arts routinely exercise judgment in determining which subjects to treat and which treatments to use on them: the skilled physician recognizes extreme limitations, so those examples do not demonstrate that 'undue experimentation' is required in practicing the claimed invention.

The enablement analysis should be focused on the challenged claim and the proper legal standards. The claim says this:

20. A method to treat conditions associated with unwanted activity of TGFβ which method comprises administering to a subject in need of such treatment an effective amount of the compound of claim 1 or a pharmaceutical composition thereof.

The legal standard requires one of ordinary skill to be able to practice the invention as claimed without 'undue experimentation.' The case law states that a significant amount of experimentation may be required as long as it is routine. According to *Wands* (8 USPQ2d 1400) "the key word is 'undue' not 'experimentation'," and "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Thus the question is whether the enablement provided is commensurate in scope with the claims, and whether one of ordinary skill could practice the invention without 'undue' (non-routine) experimentation using guidance from the specification and the knowledge and skills of the ordinary practitioner.

Based on the specification, one of ordinary skill could identify a condition to be treated: it would be one where TGF-β activity is too high, and the specification provides a list of conditions where that may occur. Methods for determining TGF-β activity levels in a subject were well known in the art before the application was filed; thus one of ordinary skill could readily identify a subject in need of treatment for excessive levels of TGF-β activity.

The specification provides ample evidence to show that the claimed compounds are effective to reduce the level of activity of TGF-β: over 150 active compounds are disclosed. Thus one of ordinary skill could readily identify a suitable compound for use in the claimed methods.

Determining an effective amount of a compound to use is well within the ordinary skill: it requires only the selection of a starting dosage, and means to determine whether that dosage effects a reduction in the subject's TGF-β activity level or a symptomatic improvement. That type of optimization is required for even the best understood treatments:

my wife and her doctor monitor and adjust dosage levels for her arthritis medication on a regular basis to achieve a dosage that works. That step is routine.

The experimentation required to determine whether a TGF-β inhibitor is appropriate is not undue: it may include recognition of a condition likely to be benefited by a TGF-β inhibitor, such as those identified in the specification, and perhaps a routine assay to measure the subject's TGF-β levels during treatment. The specification provides extensive guidance in the selection of a suitable compound for inhibiting the activity of TGF-β. And the optimization of a drug dosage is routine in the art. Therefore, one of ordinary skill could practice the claimed invention without undue experimentation. Accordingly, the applicant requests reconsideration and withdrawal of this rejection.

The Rejections Under 35 U.S.C. § 102

All claims other than claim 19 were rejected over Cai, WO 02/47690. Cai allegedly teaches compounds within the scope of original claim 1; however, all of the potentially relevant compounds in Cai are believed to have a phenyl or indolyl group as the element corresponding to Ar in formula (1). The Office found claim 19, which requires Ar in formula (1) to be a 4-pyridyl group, novel over Cai. The claims have now been amended to limit Ar in formula (1) to exclude phenyl, so the claims are distinuguished from the few cited compounds in Cai having phenyl in this role. Cai apparently discloses only one indolyl derivative. The indole derivative, compound 166 (pg. 151) in Cai, has a pyridyl group at position 2 of its pyrimidine ring. Therefore, it is not a compound of formula (1) in the present claims, so Cai does not anticipate the claims. In light of the amendment, the rejection over Cai can be withdrawn.

The claims other than claim 19 were also rejected over Davies, WO 02/22067, which also allegedly discloses compounds within the scope of the original claims. Davies describes "Pyrazole compounds useful as protein kinase inhibitors." Title and abstract of Davies. The pyrazole present in all of the Davies compounds corresponds to Ar in formula (1) of the present claims. The claims have been amended to list specific heteroaryl groups for Ar, none

of which is a pyrazole. Therefore, the present claims are novel over Davies, and the rejection based on Davies can be withdrawn.

Claims 1-19 were rejected over Kleeman, US 5,849,758, which allegedly discloses some compounds within the scope of the original claims. The compounds disclosed in Kleeman all appear to have O (oxygen) in the position corresponding to X in formula (1). The claims have been amended to limit X in formula (1) so that it cannot be O. As a result, the compounds in the present claims are novel over Kleeman, so the rejection over Kleeman can be withdrawn.

In light of the claim amendments discussed above, the claims are believed to be novel over each of the cited references. Therefore, these anticipation rejections can be withdrawn.

The Rejections Under 35 U.S.C. § 103

The original claims were rejected as obvious in light of each of three separate references, Cai, Davies, and Kleeman (*i.e.*, each rejection is based on a single reference). The rejections are moot in part, in light of the present amendments clearly distinguishing the claimed genus from each reference. However, the applicant traverses the rejections to the extent they could be applicable to the amended claims.

To establish a *prima facie* obviousness rejection, the Office must show "some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings....The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure." MPEP 2143, citing *In re Vaeck*, 20 USPQsc 1438 (Fed. Cir. 1991). That standard cannot be met using any of these references with respect to the amended claims, for at least the following reasons.

Cai: All claims were rejected as obvious over Cai. The Office alleged that some compounds disclosed in Cai fall within the scope of the original claims. The applicant believes that the amended claims do not read on any compounds disclosed by Cai.

The Office then said:

> "Cai et al. teaches the equivalency of those compounds exemplified with specific substituents with that generically recited on page 10-12 for Formula I-III See formula I-III and note the definition of various variable groups include several compounds. Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make pyrimidine compounds variously substituted with Ar_1, Ar_2, R_1, R_2, and R_3 as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above."

Though this passage is not entirely clear to the applicant, it seems to say that all compounds within the broadest generic shown in Cai would be equivalent to those actually exemplified in Cai, and are thus unpatentably obvious; or it may intend to say that all possible options for any particular element are taught to be equivalent because they are included in the Cai genus.

The Office's position seems to suggest that all embodiments of each variable in the Cai genus are 'equivalent' within the context of the reference, which is clearly not the case: the reference demonstrates that they are not equivalent and expresses 'preferences' for certain embodiments of the variables, both implicitly (by disclosing activity differences) and expressly (by disclosing preferred embodiments of some variables, as further discussed below.) The Examiner lists no fewer than five variables, Ar_1, Ar_2, R_1, R_2, and R_3 from Cai, and seems to suggest that all conceivable combinations of all embodiments of all of those variables would result in compounds that are unpatentably obvious.

The legal standard for establishing a *prima facie* obviousness rejection requires far more than that, though. (MPEP 2144.08 § II: "The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness.") The disclosure of various separate features does not render a claim obvious if the reference does not suggest the particular combination claimed. ("In making an obviousness determination, Office personnel should consider the number of variables which must be selected or modified, and the nature and significance of the differences between the prior art and the claimed invention." MPEP 2144.08 II.A.4(c).) Thus a subgenus within Cai can be nonobvious and thus patentable over Cai, if Cai provides no disclosure of or guidance toward that subgenus. See, e.g., MPEP 2144.08, esp. section II, which specifically relates to

obviousness analysis in chemical inventions.) Cai provides no guidance toward the features of the present claim; in particular, it provides no suggestion to make compounds having a 2-phenyl on a pyrimidine in combination with any of the groups that Ar can represent in the present claims.

A claimed genus must be analyzed as a whole, and can be patented even if it overlaps with a genus from a reference. The alleged obviousness or disclosure of any single limitation of a genus claim is not sufficient for an obviousness rejection of a chemical genus. See MPEP 2144.08. That is especially true when the genus in the disclosure includes many variables so that it discloses a large number of different combinations. A reference must suggest the particular combination of limitations contained in a claim to render the claim unpatentably obvious; it is not enough to just disclose the separate features. Thus, even if the present claims were drawn to a subgenus within Cai—which they are not—that subgenus would not be rendered obvious by Cai unless Cai suggested it, which it does not.

The claimed compounds have a phenyl group at position 2 of the pyrimidine ring, while only a handful of the compounds in Cai have that feature. Cai clearly suggests that heterocycles are preferred in that position, since nearly all of the compounds shown in Cai have a heterocycle there. (The table on pages 139-152 shows about 100 compounds, of which about 4 have a 2-phenyl group. Most have either pyridyl or pyrazinyl at position 2, consistent with the statement in Cai describing "especially preferred compounds of formula I [which] include compounds wherein Ar_1 is optionally substituted pyridinyl, pyrimidiyl and pyrazinyl." (Cai at paragraph [0022]: Note: Ar_1 in Cai corresponds to the group at position 2 of the pyrimidine ring.)

Similarly, Cai clearly teaches that a phenyl is preferred as the aryl portion of the substituent at position 4 of the pyrimidine compounds (see the Preferred structure III on page 12 of Cai, for example). Among all of the compounds in the table in Cai on pages 139-152, only a few have an aryl group other than phenyl ring attached to the linking nitrogen atom that most nearly corresponds to X in formula (1). That group corresponds to Ar in formula (1) of the present claims, which cannot be phenyl in the claims as amended. The few compound having a non-phenyl as Ar^1 in Cai have a pyridinyl or indolyl group there. And

all of those have a pyridyl group at position 2 of the pyrimidine ring, so they do not fall within formula (1) as presently claimed.

The compound genus as presently claimed thus combines two structural features--a phenyl group at position 2 of a pyrimidine, and a heteroaryl group linked through N to position 4 of a pyrimidine--neither of which Cai suggests is desirable. Cai viewed as a whole, with its preferred subgenus and exemplified embodiments, provides no motivation to make compounds having this combination of features. Indeed, it effectively teaches away from the *combination* in the presently amended claims.

Finally, nothing in Cai provides a reasonable expectation of success with the presently claimed compounds. There is no suggestion to make the combination of features claimed, and no reason to expect that such compounds would be active if made. Therefore, in light of the amendment to the claims, this rejection should be withdrawn.

Davies: Claims 1-18, 20 and 21 were also rejected as obvious over Davies. The analysis appears to be the same as that relied on to reject over Cai. As with Cai, the amended claims have no overlap with the compounds exemplified in Davies. Davies apparently only teaches compounds having pyrazole or benzopyrazole as the group corresponding to Ar in formula (1): it does not teach or suggest the combination of structural features of the present invention. Also, as with Cai, nothing in Davies provides any motivation to make compounds having the combination of features of the compounds of the amended claims. It does not suggest the desirability of making compounds with any of the claimed heteroaryl groups as Ar in a compound of formula (1) in the present claims. Thus Davies does not provide motivation to modify what it does teach to arrive at the invention as presently claimed. Finally, the pyrazole compounds of Davies do not provide any expectation that compounds having other heterocycles as the Ar group in a compound of formula (1) as presently claimed will be active. Thus in light of the amendments, Davies provides none of the elements of a *prima facie* case for an obviousness rejection, and this rejection can be withdrawn.

Kleeman: Claims 1-19 were rejected as obvious over Kleeman, using a similar analysis to that applied to Cai. Again, as with Cai and Davies, the present claims have been amended to exclude all compounds disclosed in Kleeman. Kleeman apparently does not

disclose any compounds having NR^1 or S as the structural element corresponding to X in formula (1) of the present claims, for example, nor does it provide any suggestion or motivation to modify what it discloses to produce such compounds. All of the compounds it provides activity data for in the Tables have oxygen as the structural element that most nearly corresponds to X in formula (1) of the present claims. Thus, even if compounds having X = S were suggested, the reference provides no suggestion regarding what choices to make for the many other variables present. Nor does the reference provide a reasonable expectation of success for the combination of features presently claimed, since none of its data suggests that such compounds would be active. Thus Kleeman does not render obvious the claimed genus for at least these reasons, and this rejection can also be withdrawn.

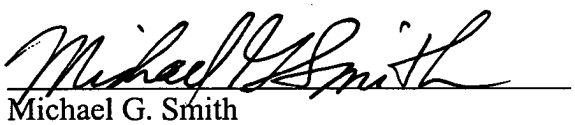
Conclusion

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejections of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No **Deposit Account No. 03-1952** referencing docket No. 219002029400.

Respectfully submitted,

Dated: January 12, 2006

By: 

Michael G. Smith
Registration No. 44,422

MORRISON & FOERSTER LLP
3811 Valley Centre Drive, Suite 500
San Diego, California 92130-2332
Telephone: (858) 720-5113
Facsimile: (858) 720-5125